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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/257,650 | 02/25/1999 | MASAHIKO FUJINO | 48194 | 2632 |

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EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

| EXAMINER | |
|---|---|
| O HARA, EILEEN B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 28 |

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/257,650 | Applicant(s) FUJINO, MASAHIKO | |
|---|---|---|---|
| | Examiner Eileen O'Hara | Art Unit 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13, 18, 19, 22, 23, 26 and 28-44* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,22,23,26 and 28-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13, 18, 19, 22, 23, 26 and 28-44* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *27* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 1-13, 18, 19, 22, 23, 26 and 28-44 are pending in the instant application. Claims 18, 19, 22, 26, 28-31, 33, 35, 36 and 44 have been amended, claims 14, 16, 17, 21, 24 and 27 have been canceled as requested by Applicant in Paper Number 26, filed March 6, 2003.

Claims 1-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 18, 19, 22, 23, 26 and 28-44 are currently under examination.

### *Withdrawn Objections and Rejections*

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

### *Claim Objections*

3. Applicant is advised that should claim 31 be found allowable, claim 36 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 26 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26 and 34 are indefinite because claim 43 encompasses a screening method for a synthetic substance which will activate an aberrant receptor but will not activate a normal receptor, and claim 26, which depends from claim 43, recites that "the substance normally operates said receptor", and it is not clear how a synthetic substance "normally operates" an aberrant receptor, since such a substance would not be a naturally occurring ligand.

### *Rejections Over Prior Art*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 18, 19, 22, 23, 26 and 28-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., or Birnbaumer et al., or Green et al., or Kong et al., in view of Choong et al., and further in view of Dower et al., all previously of record, for reasons cited in the previous Office Action, Paper No. 24, at pages 9-10. The teachings of Dower et al. were

discussed in Paper No. 24, and the teachings of the other references in Paper Nos. 12, 16, 18, 20 and/or 24.

Applicants have canceled claims 14, 16, 17, 21, 24 and 27 and changed dependencies of other claims, thereby overcoming the rejections under 35 U.S.C. 102(b). The claims as amended now are rejected under 35 U.S.C. 103(a).

Applicant traverses the rejection and on page 6 of the response assert that while one of ordinary skill in the art would look to other type of receptors to gain information to study a receptor of interest (e.g., an insulin receptor), it is well-established law that the mere fact that references can be combined is not enough, and there must be a "suggestion or motivation in the reference to do so.", and the prior art must suggest the desirability of the combination. Applicant asserts that in previous responses, the two references each address a different disease and a different receptor, and there would be no reason for one of ordinary skill in the art that was studying an insulin receptor mutation to look for an article addressing an androgen insensitivity, and to combine the teachings of the two references would render to goal of Lebrun et al., to study the insulin receptor, unattainable.

Applicants' arguments have been fully considered but are not deemed persuasive. M.P.E.P. 2143.01 states:

> "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313,

1317 (Fed. Cir. 2000)."

Lebrun et al. teaches screening for compounds that would activate an insulin receptor that has a mutation that impairs the ability of the hormone to activate autophosphorylation of receptors and phosphorylation of substrates, the mutation not affecting the ligand binding extracellular portion of the receptor. One of ordinary skill in the art would have been motivated to use the screening assays of Lebrun et al. with an insulin receptor that had a mutation that affected ligand binding, even in the absence of a second reference that teaches a receptor with a mutation in the ligand binding domain, (e.g., Choong et al.), because one of ordinary skill in the art would want to screen for drugs that could be used therapeutically to treat individuals that had such a mutant insulin receptor. The Choong et al., Green et al., Kong et al. and Birnbaumer et al. references demonstrate how common mutations in the ligand binding domain of receptors are, and that such mutant receptors are used to screen for compounds that would bind to and activate them. One of ordinary skill in the art would appreciate from reading such articles that use screening methods to find agonists for receptors that have mutations in the ligand binding domains, that the same screening assays could be used for an insulin receptor having a mutation in the receptor binding domain.

On pages 8-9 of the response, Applicant argues that the symptoms of congenital nephrogenic diabetes insipidus (CNDI) could be relieved by frequent administration of dAVP, and this result shows the reduced affinity of the receptor for AVP, but does not show the ability of a compound to operate the aberrant receptor in a manner similar to a non-aberrant receptor, and points out that the Examiner admits that Birnbaumer et al. did not find a compound that

caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, as present claimed.

Applicant's arguments have been fully considered but are not deemed persuasive. As discussed in the previous Office Action, Paper No. 24 at page 4, while Birnbaumer et al. did not find a compound that caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, that is not the relevant issue. It is the method steps that are relevant, and the result obtained in the prior art using those method steps is not relevant. The assay method of Birnbaumer et al. *would* be able to find a compound that caused the mutant type-2 vasopressin receptor to operate in a manner similar to the wild-type receptor, if other compounds were screened.

On page 8 of the response, Applicant argues that Green et al. did not test compounds to determine their effect on the activity of the mutant and wild-type receptors, but rather, merely tested their binding affinities for each of the receptors, and that the Examiner's finding that dopamine had the same effect on both the wild type and mutant receptor is not accurate and does not render the presently claimed invention obvious.

Applicant's arguments have been fully considered but are not deemed persuasive. The function of the wild type and mutant receptors was also assayed using different compounds, in which adenylyl cyclase activity was assayed (abstract, page 23117, first column , 2nd full paragraph, paragraph bridging page 23117 and 23118 to page 23119, first column, first paragraph, and page 23121, first column, first full paragraph).

On page 9 of the Office Action, Applicant asserts that Figure 2 shows the use of 1 uM of opioid antagonists, and such a high concentration of antagonist is not realistic in this type of

experiment and one of ordinary skill in the art would not be motivated to use the teachings of Kong et al. to obtain the methods of screening that are presently claimed.

Applicant's arguments have been fully considered but are not deemed persuasive. The Kong et al. reference shows that one of ordinary skill in the art would typically use a receptor with altered ligand binding to screen compounds that could bind and activate it.

Applicant on pages 9-14 of the response asserts that Dower et al. teach the screening of compounds by measuring the binding of screened compounds to the receptor, but Dower fails to teach the measurement of the operation activity of the receptors of interest, and that, and fails to make up for the deficiencies in the other cited references. Applicant asserts that there is no motivation or suggestion in any of the references to combine the teachings of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al, in view of Choong et al., which simply fail to teach the desirability of screening large libraries of compounds for binding with their receptors of interest, and there would be no motivation to look to Dower et al. in the first place, and even if one of ordinary skill were motivated to combine any of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al, in view of Choong et al.. Applicant further asserts that with Dowever et al., the methods of the present invention would not have been obvious from those teachings, and that at most, Dower would provide for a method of tagging different reactions with a peptide of interest for further identification.

Applicant's arguments have been fully considered but are not deemed persuasive. Dower et al. was cited to show that it was well-known in the art at the time of the invention that the types of compounds that could be screened for therapeutic purposes could be synthetic compounds, and that such screening could be done with combinatorial libraries. In several

places, Dower et al. states that such compounds could be useful, for example as pharmacological agents. Pharmacological agents would not just bind, but would produce a useful, functional activity. For example, at column 2, lines 38-48, Dower et al. states:

"High throughput screening of collections of chemically synthesized molecules and of natural products (such as microbial fermentation broths) has traditionally played a central role in the search for lead compounds for the development of new pharmacological agents. The remarkable surge of interest in combinatorial chemistry and the associated technologies for generating and evaluating molecular diversity represent significant milestones in the evolution of this paradigm of drug discovery. See Pavia et al., 1993, Bioorg. ed. Chem. Left. 3: 387-396, incorporated herein by reference."

In column 2, lines 57-60:

"Moreover, the potent and specific biological activities of many low molecular weight peptides make these molecules attractive starting points for therapeutic drug discovery."

In column 4, lines 59-65:

"The invention also relates to methods for screening encoded synthetic libraries to identify useful compounds. In one important aspect, the invention provides important advances in the field of natural product screening relating to methods for generating, tagging, and screening natural product libraries to characterize and identify compounds with useful activity."

At column 31, lines 16-23, Dower et al. states:

"By way of example, such libraries can be used in assays to identify ligands that bind receptors, such as peptides and nucleic acids that bind to proteins, drugs that bind therapeutic target receptors, and epitopes (both natural and synthetic) recognized by antibodies, as well as to identify a variety of compounds with pharmaceutical, agricultural, and medical diagnostic applications."

Thus, one of ordinary skill in the art at the time of the invention would have been motivated to use the combinatorial chemistry screening methods of Dower et al., in which large numbers of synthetic (or natural) compounds could be rapidly and easily screened, in the

receptor assays of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al, in view of Choong et al., in order to discover compounds that could activate a mutant receptor that could not be activated by the normal ligand, in order to find useful pharmaceuticals to treat diseases or disorders.

M.P.E.P. 2143.01 states:

"The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313,1317 (Fed. Cir. 2000). See also > In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references);< In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made use the screening methods of Birnbaumer et al., or Green et al., or Kong et al., or Lebrun et al. in view of Choong et al. to screen large libraries of synthetic compounds made by combinatorial chemistry, as taught by Dower et al. The skilled artisan would be motivated to do so in order to rapidly screen large numbers of compounds that could bind to and activate an aberrant receptor in order to discover new compounds with desired pharmacological properties, as taught by Dower et al. There would be a reasonable expectation of success, since the generation and screening of combinatorial libraries has been widely and successfully used in the field of drug discovery.

***Conclusion***

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

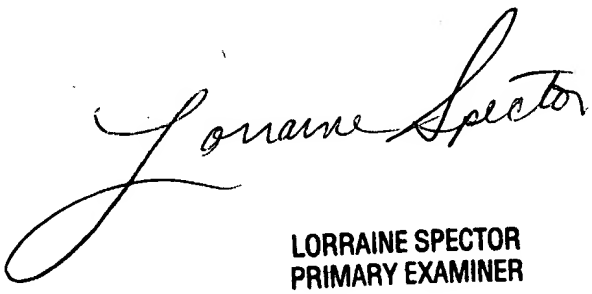
Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner



LORRAINE SPECTOR
PRIMARY EXAMINER